Section of Radiology

President J W D Bull MD

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Management of Malignant Melanoma [*Abridged*]

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Regression of Malignant Melanoma as a Manifestation of a Cellular Immunity Response

Cases of malignant melanoma with multiple skin metastasis are not always uniformly progressive. In some cases the condition appears to remain stationary for years; old lesions die off and new ones appear. When a lesion like this involutes, it dries up and a crust falls off, leaving a pink mark. Microscopical section may show a few residual malignant melanocytes in the dermis, together with increased vascularity, well-marked round cell infiltration and many melanophages, the result of previous activity. Regression is more commonly seen in part of a malignant melanoma, as for instance when part of the pigmented patch blanches. Such tumours have a better than average prognosis. Regression or involution of a malignant melanoma can be explained in terms of cellular immunity.

Three stages in the development of malignant melanoma have been described (Lloyd 1954, 1964, Petersen *et al.* 1962). These stages are based on the degree of invasion, but they also represent degrees of malignancy.

Stage 1 is malignant melanoma 'in situ', with no invasion of the dermis. In the superficial dermis there is usually an intense round cell infiltration, consisting of lymphocytes, plasma cells and melanophages. It does not metastasize, but may develop into the next stage.

Stage 2: There is invasion by melanocytes of the superficial dermis. The round cell reaction is usually still intense. It is generally basal to the tumour and does not diffusely infiltrate it. The prognosis is very good and lymphatic metastasis is only 8%.

Stage 3: A tumour develops within or on the edge of the pigmented patch. This tumour may excite hardly any lymphocytic reaction itself, but the reaction to its pigmented halo may become more intense, and there may be regression of the malignant process there, the melanocytes returning to normal. The pattern of lymphocytes around the tumour is basal, not diffuse, and patchy, not continuous.

This regression of malignant process is a common finding in primary malignant melanoma, but it is unusual to see it actually occurring. Fig 1 illustrates the process. The acinar buds of melanocytes proliferating in the basal epidermis become loosened, invaded by lymphocytes and disappear. This picture is from the pigmented halo of a Stage 3 malignant melanoma of the foot in a woman of 71. Regression or inhibition of melanocytes is particularly likely to occur when

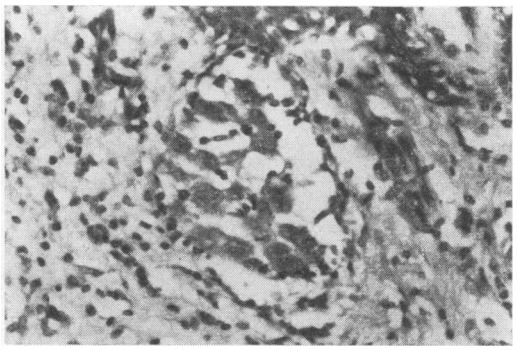

Fig 1 *Regression of malignant pigmented flare in process.* ×*150*

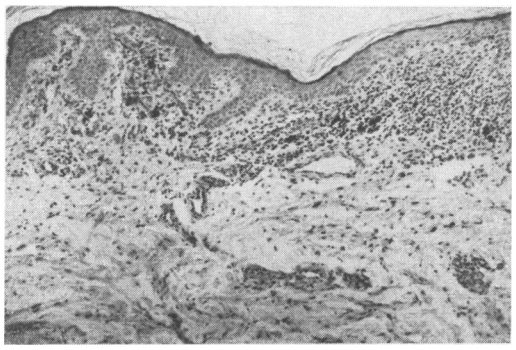

Fig 2 *Completed regression in the superficial part of a malignant melanoma.* × *66*

the tumour develops from one stage to another. Thus Stage 2 invasion may be followed by inhibition of the remaining Stage 1 pieces of pigmented flare; or Stage 3 tumour formation may result in regression not only of the Stage 1, but of the Stage 2 bits of pigmented flare.

When histologists meet this phenomenon in a biopsy of part of a melanoma, they are often puzzled. More than once I have seen a recurrent malignant melanoma, and on reference to the original sections reported elsewhere have found regression of the Stage 1 or 2 part of a malignant melanoma, the significance of which had not been appreciated. But such appreciation may work the other way. A woman of 43 had many pigmented nævi. One of them, which appeared two months previously, increased in size and was biopsied. Fig 2 shows involution of a pigmented flare. I said there was probably frank malignancy round the corner and the lesion was excised. Further sections showed the same superficial change, but deep in the dermis was one small patch of invasive malignant melanoma.

The fact that even invasive and destructive lesions can regress is shown in the case of a woman of 27 who had a two-year history of a growing pigmented lesion of the lower leg, with weeping and irritation (typical malignant history), but for the last six months it had been getting flatter again. Fig 3 shows part of the still active tumour, probably regressing, since it is diffusely infiltrated with round cells. Fig 4 shows part of the same lesion where regression is complete. In the affected area can be seen a destroyed hair follicle.

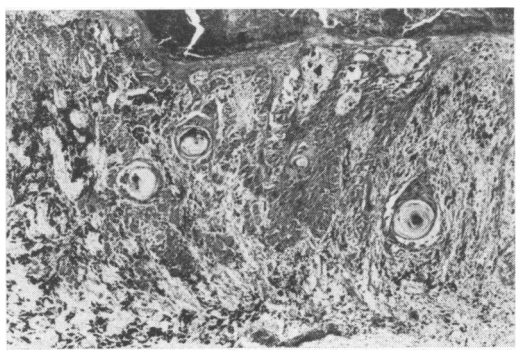

Fig 3 *Regressing tumour.* × *33*

This cellular reaction is seen in some examples of two other kinds of melanoma, both benign, which have a natural tendency towards spontaneous regression. One is the benign juvenile melanoma of Spitz, the other is Sutton's halo nævus.

Conclusion

The lymphocytic infiltration is part of the cellular immunity response of the host to the tumour.

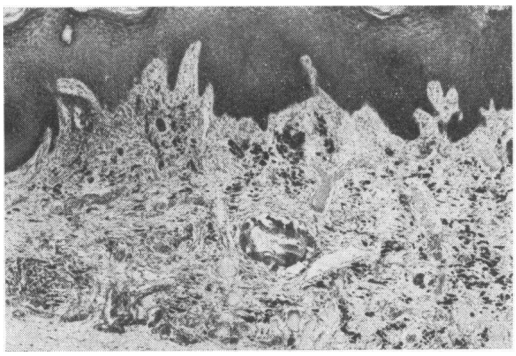

Fig 4 *Same case as Fig. 3. Complete regression of part of a Stage 2 malignant melanoma, which had caused destruction of a hair follicle.* × *33*

When the tumour becomes more malignant the cellular response alters, either increasing (Stage 2) or decreasing (Stage 3), or disappearing (many metastases). But the alteration in the nature of the tumour antigen sometimes has the effect of producing a cellular response which is so much more intense that it causes involution of the less malignant remaining parts of the lesion.

It is unusual to find spontaneous regression of the whole tumour (about 3·5% of our cases). The body does not seem to wish to get rid of its tumours, but only to live at peace with them. But when it does occur, the regression takes the same form as that seen in partial involution of other malignant melanomas: diffuse round cell infiltration, the disappearance of the malignant melanocytes, the reappearance of the normal epidermal melanocytes and the persistence of much of the old, shed pigment.

The lesson to be drawn by radiotherapists is not to irradiate malignant melanomas which are more or less stationary, as, by so doing, the immunological forces which are maintaining the balance may be destroyed.

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Radiation Dosimetry of Intralymphatic Radiotherapy

The fate of radioisotopes infused into the lymphatics was investigated in two groups of patients. In the first group, scintiscanning was used to observe the whole body distribution of therapeutic quantities of iodine-131 Lipiodol and particular attention was given to the dose received by the lungs. In the second group of patients, lymph nodes were surgically removed following the infusion of either ^{131}I Lipiodol or colloidal gold-198, and the relative positions of the radioactivity and tumour in these nodes were determined.

WHOLE BODY DISTRIBUTION OF THERAPEUTIC DOSES

As a prophylactic treatment following local excision of primary malignant melanoma from the lower limbs, 15 patients were each given an intralymphatic infusion of Lipiodol Ultra-Fluid containing ^{131}I-labelled triolein (LUF) using Kinmonth's technique (Kinmonth *et al.* 1955). None of the patients had any clinical evidence of tumour dissemination at the time of the infusion. The total volume of inactive plus radioactive Lipiodol infused was not more than 5 ml and was administered at a rate not exceeding 0·1 ml/min. Lugol's iodine was given orally to suppress any possible thyroid uptake.

The radioactivity was observed with a whole body scintiscanner (IDL Type 6082), fitted with a detector containing a small sodium iodide crystal and a single-hole collimator. Initially the whole of each patient was scanned and subsequently the regional nodes and the chest were both repeatedly scanned for at least a week. The scans consisted of a number of marks, each one produced by a selected number of detected rays. By counting the number of marks on each scan, the rate of loss of radioiodine from the regional nodes and the chest was measured. Measurement of the activities in the nodes was not attempted because the sensitivity of the detector was depth dependent.

To estimate the activities in the lungs, experiments were performed with 'phantoms' containing known activities of ^{131}I and composed of 'lung equivalent' material having a density of 0·33. Data were obtained on the effect of varying the air gap between the detector and the 'skin', the thickness of the 'chest wall' and the 'lung', and also the lung density, published values of which vary from 0·3 (Tow *et al.* 1966) upwards.

The Scans

No radioactivity was detected in the liver or thyroid of any patient and only small amounts were observed in the legs or near the sites of lymphatic cannulation. The regional nodes were clearly delineated (Fig 1). Sufficient data were

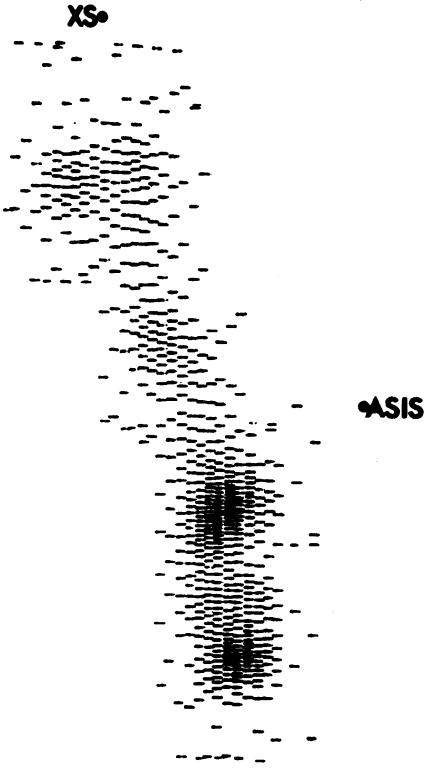

Fig 1 *Scan of regional nodes.* XS, *xiphisternum.* ASIS, *anterior superior iliac spine*